National Cancer Institute

Cancer Risk in Adults Undergoing Radiotherapy

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Background: Ionizing Radiation

Ionizing radiation exposures	Magnitude of doses
Chest x-ray (chest)	0.0001 Gy
Mammogram (breast)	0.003 Gy
Abdominal CT scan (abdomen)	0.1 Gy
Radiotherapy	
Scatter to nearby organs	1-9 Gy
Tumor dose	10-70 Gy

Background: Radiotherapy

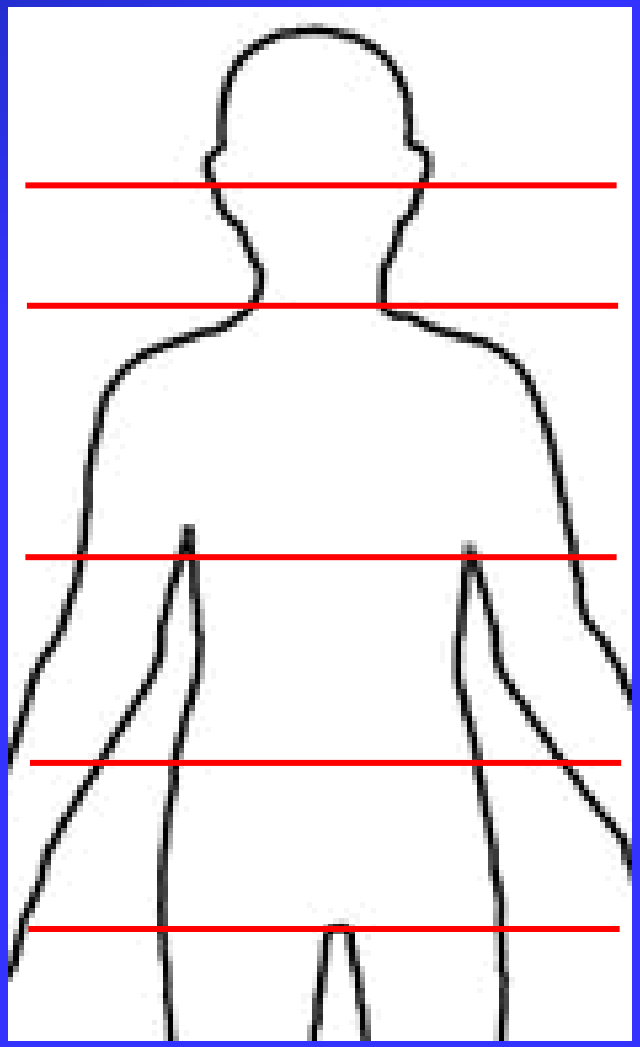
Benign conditions

Tinea capitis
Hemangioma

Breast disease
Ankylosing spondylitis

Peptic ulcer disease

Gynecologic disease



Cancer treatment

Brain/CNS

Oral cavity, Pharynx
Thyroid, Larynx

Female breast

Hodgkin lymphoma

Testes (seminoma)
Cervix, Endometrial
Prostate, Anus

Background: Research Focus and Implications

- Magnitude of risk at higher doses
- Shape of the radiation dose-response relation
- Modifiers of radiotherapy-related risks
  - Age at exposure
  - Time since exposure
  - Attained age
  - Other cancer risk factors

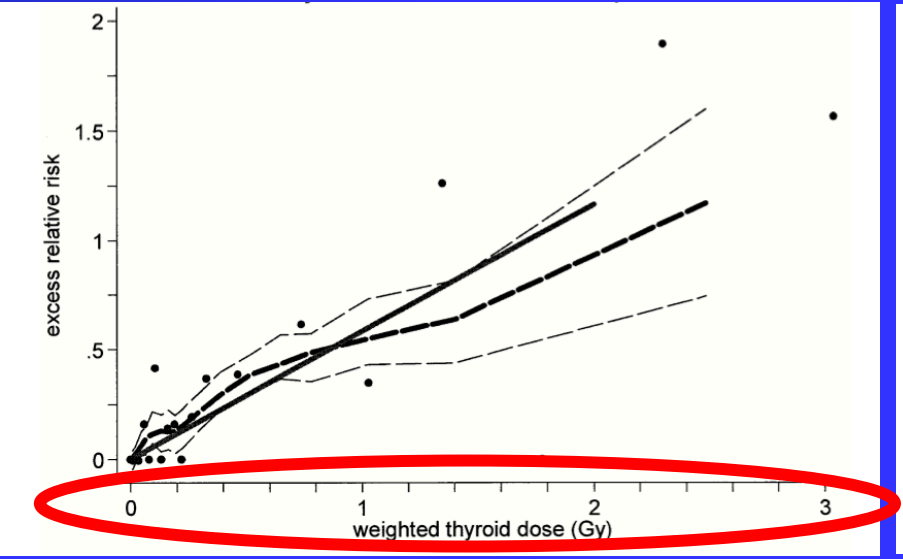
Background: Research Focus and Implications

- Biology
  - Cancer etiology
  - Mechanisms of carcinogenesis
- Clinic
  - Risk/benefit assessment for radiotherapy treatment
  - Long-term health of patients

Background: Examples

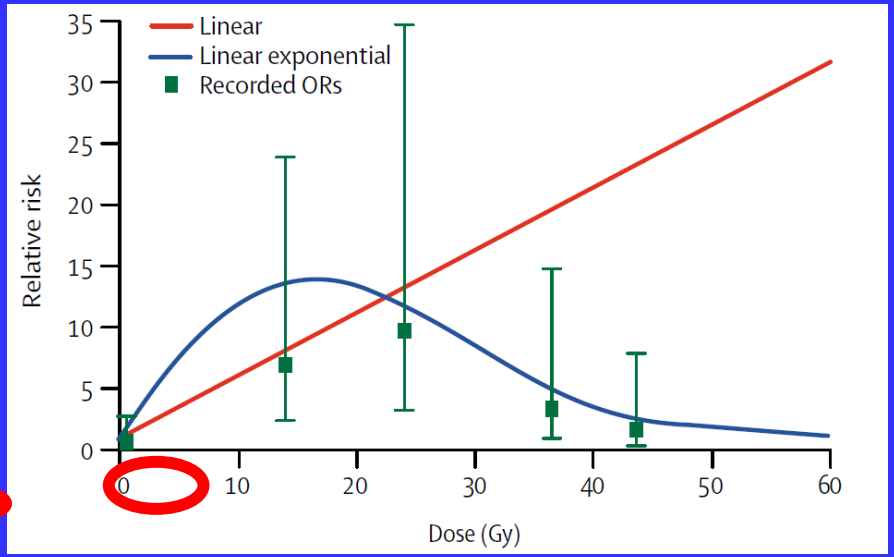
- Importance of understanding dose-response relations across a wide range of doses

Thyroid cancer risk among atomic bomb survivors



Preston et al. Radiat Res 2007

Thyroid cancer risk after radiotherapy for childhood cancer



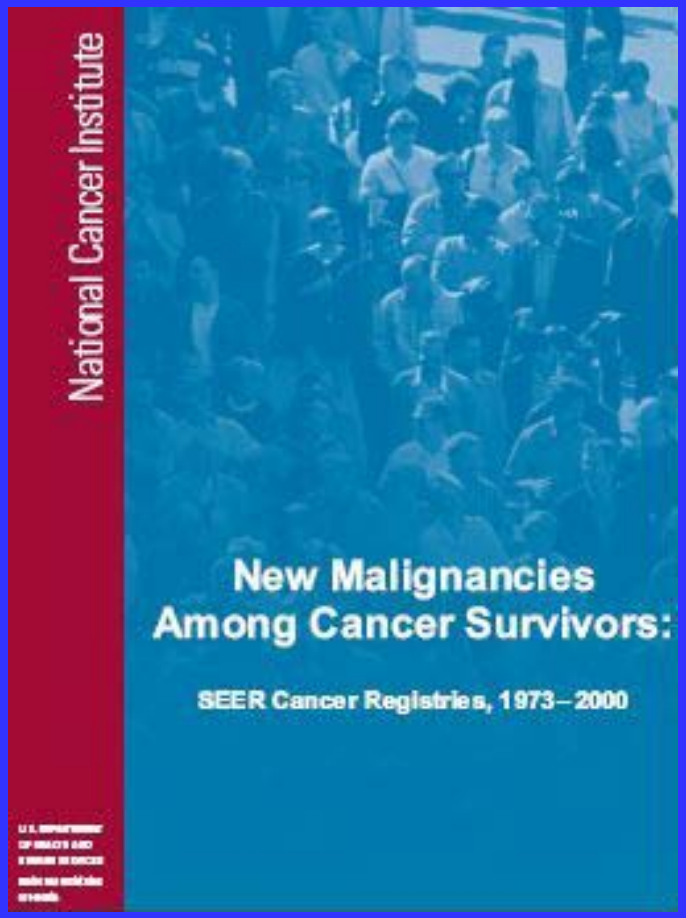
Sigurdson et al. Lancet 2005

Outline

- Study design
- Radiotherapy associated with increased risk of:
  - Highly radiosensitive malignancies
    - Leukemia
    - Breast
  - Other cancers
    - Lung
    - Upper gastrointestinal cancers (esophagus, stomach, pancreas)
- Future directions

Incidence of New Malignancies among Cancer Survivors

- ✦ Data from population-based cancer registries
- ✦ Long term follow-up (30+ yrs)
- ✦ Large sample size
- – No detailed treatment information
- – No information on risk factors



Descriptive Study: Example

- Lung cancer risk after breast cancer RT (Zablotska and Neugut, Cancer 2003)
- 9 SEER registries, 1973-1998
- 260,541 women, 29% treated with RT

Time since breast cancer	Post-mastectomy RT		Post-lumpectomy RT	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
5-9 years	1.2	1.1	1.1	1.0
10-14 years	2.1*	1.1	0.8	1.3
15+ years	2.1*	1.2	-	-

* $P<0.05$

Case-Control Studies

- ✦ Data abstracted from medical records
- ✦ Detailed treatment information
  - ✦ radiation dose-response relationship
  - ✦ possible confounding or effect modification by other treatments
- – Resource intensive
- – Minimal/incomplete information on other cancer risk factors

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Leukemia

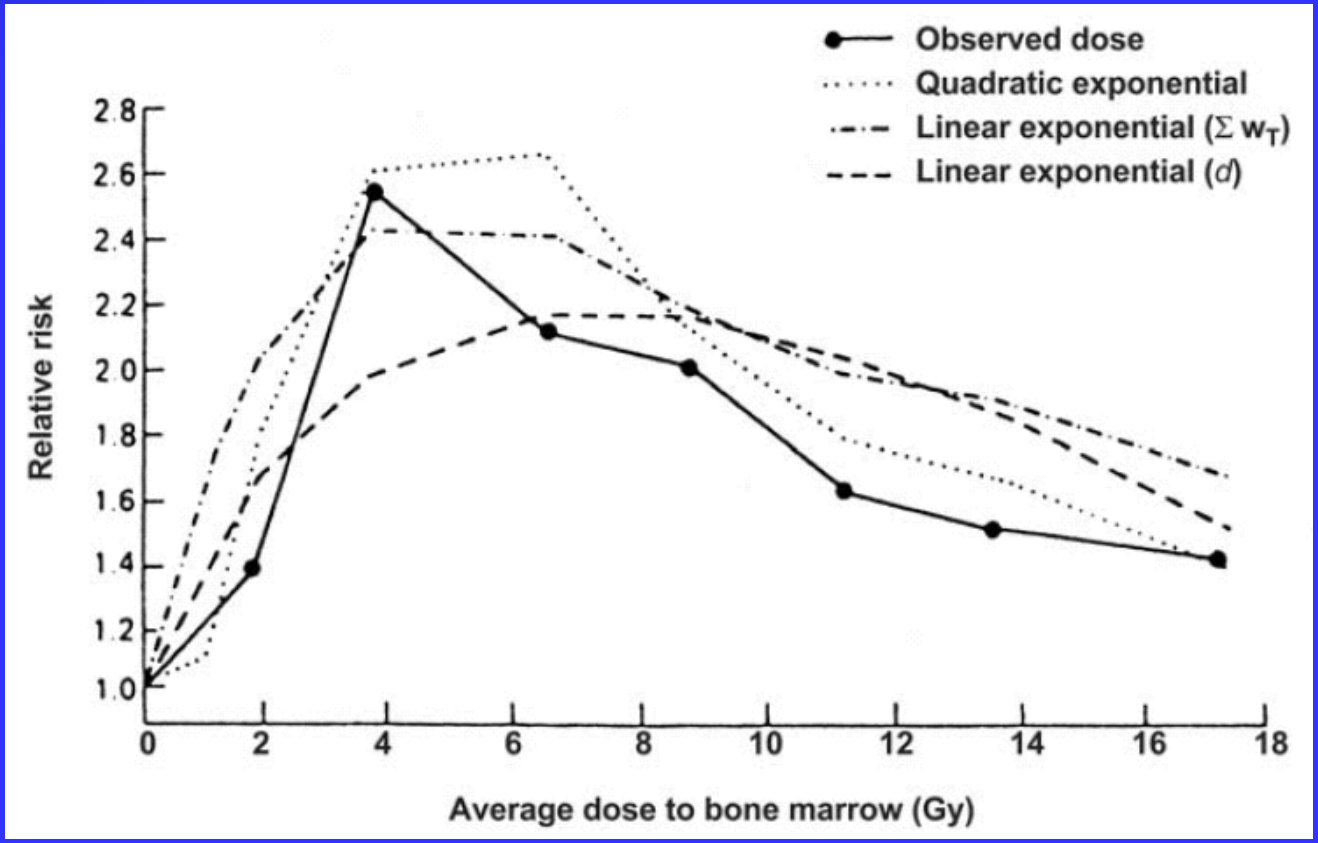
- Increased risk with radiotherapy (particularly pelvic):
  - endometrial (Curtis et al. JNCI 1994)
  - cervical cancer (Boice et al. JNCI 1987, Radiat Res 1988)
  - testicular cancer (Travis et al. JNCI 2000)
  - benign gynecologic disease (Inskip et al. Radiat Res 1993)
  - Hodgkin lymphoma (Kaldor et al NEJM 1990)
  - breast cancer (Curtis et al. NEJM 1992)

  - pooled study (Little et al. Radiat Res 1999)

Leukemia

- Lower relative risks in patients treated with radiotherapy than in the LSS
- Non-linear dose-response relation

Leukemia risk after cervical cancer (Boice et al. JNCI 1987)



Leukemia

- Disease subtypes
  - 3 radiogenic subtypes: AML risks > ALL, CML
  - ? risks for CLL
- Joint effects of radiation-related risks and:
  - Latency – Higher risks in years immediately following exposure, then declines
  - Age – Higher risks with younger age at exposure
  - Chemotherapy – conflicting

Breast Cancer

- Increased risk with chest radiotherapy:
  - ankylosing spondylitis (Weiss et al. Int J Cancer 1994)
  - mastitis (Shore et al. JNCI 1986)
  - benign breast disease (Mattson et al. JNCI 1993, Br J Cancer 1995)
  - Hodgkin lymphoma (van Leeuwen et al. JNCI 2003, Travis et al. JAMA 2003)
  - cervical cancer (Boice et al. Radiat Res 1988)
  - breast cancer (Boice et al. NEJM 1992, Storm et al. JNCI 1992; WECARE study e.g., Stovall et al. Int J Radiat Oncol Biol Phys 2008)

  - pooled study (Preston et al. Radiat Res 2002)

Breast Cancer

- Radiation dose-response consistent with linearity
  - ERR/Gy estimates range from 0.06-0.4
  - LSS ERR/Gy (overall) = 1.5 (95%CI 1.2-1.9)
- Joint effects of radiation-related risks and:
  - Age – Higher risks with younger age at exposure
  - Other treatments – reduced risk
    - Chemotherapy
    - Hormonal agents
    - Radiotherapy-induced ovarian ablation
  - Genetic susceptibility

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Lung Cancer

- Increased risk with chest radiotherapy:
  - ankylosing spondylitis (Weiss et al. Int J Cancer 1994)
  - peptic ulcer (Carr et al. Radiat Res 2002)
  - Hodgkin lymphoma (van Leeuwen et al. JNCI 1995, Travis et al. JNCI 2002, Gilbert et al. Radiat Res 2003)
- Radiation dose-response consistent with linearity
  - ERR/Gy estimates range from 0.05-0.4
  - LSS ERR/Gy (overall) = 0.7 (95%CI 0.5-0.9)

Lung Cancer

- Joint effects of radiation-related risks and:
  - Cigarette smoking – conflicting results
    - Multiplicative or supra-multiplicative (radiotherapy)
    - Additive (LSS)
  - Latency – peak risk 10-25 years after exposure
  - Age – no change in risk with increasing age
  - Chemotherapy – no change in risk with cytotoxic chemotherapy

Upper Gastrointestinal (GI) Cancers

- Radiation → risk of upper GI cancers
  - Atomic bomb survivors
  - Cancer survivors (descriptive studies)
  - Radiotherapy for benign disease (e.g., ankylosing spondylitis)
- Sparse data: magnitude of risk and dose-response relationship, effects at higher doses

➢ Second Primary GI Cancers in Cancer Survivors: An International Collaborative Study

7 Case-Control Studies

First cancer	Second Cancer: Esophagus	Stomach	Pancreas
Breast cancer	X		
Hodgkin lymphoma	X	X	X
Testicular cancer		X	X
Cervical cancer		X	

Second GI Cancers Study: Methods

- Nested case-control study
- ≥5 year survivors of breast cancer
- 5 population-based cancer registries
  - 1943-2003
  - Denmark, Finland, Sweden, Iowa, Ontario
- 316 cases with esophageal cancer after breast cancer
- 252 (80%) with available medical records

Morton *et al.*, Submitted

Second GI Cancers Study: Methods

- 488 controls with breast cancer only, individually matched to cases (2:1)
  - Cancer registry
  - Age at breast cancer diagnosis (± 5 years)
  - Calendar year of breast cancer diagnosis (± 5 years)
  - Latency

Morton *et al.*, Submitted

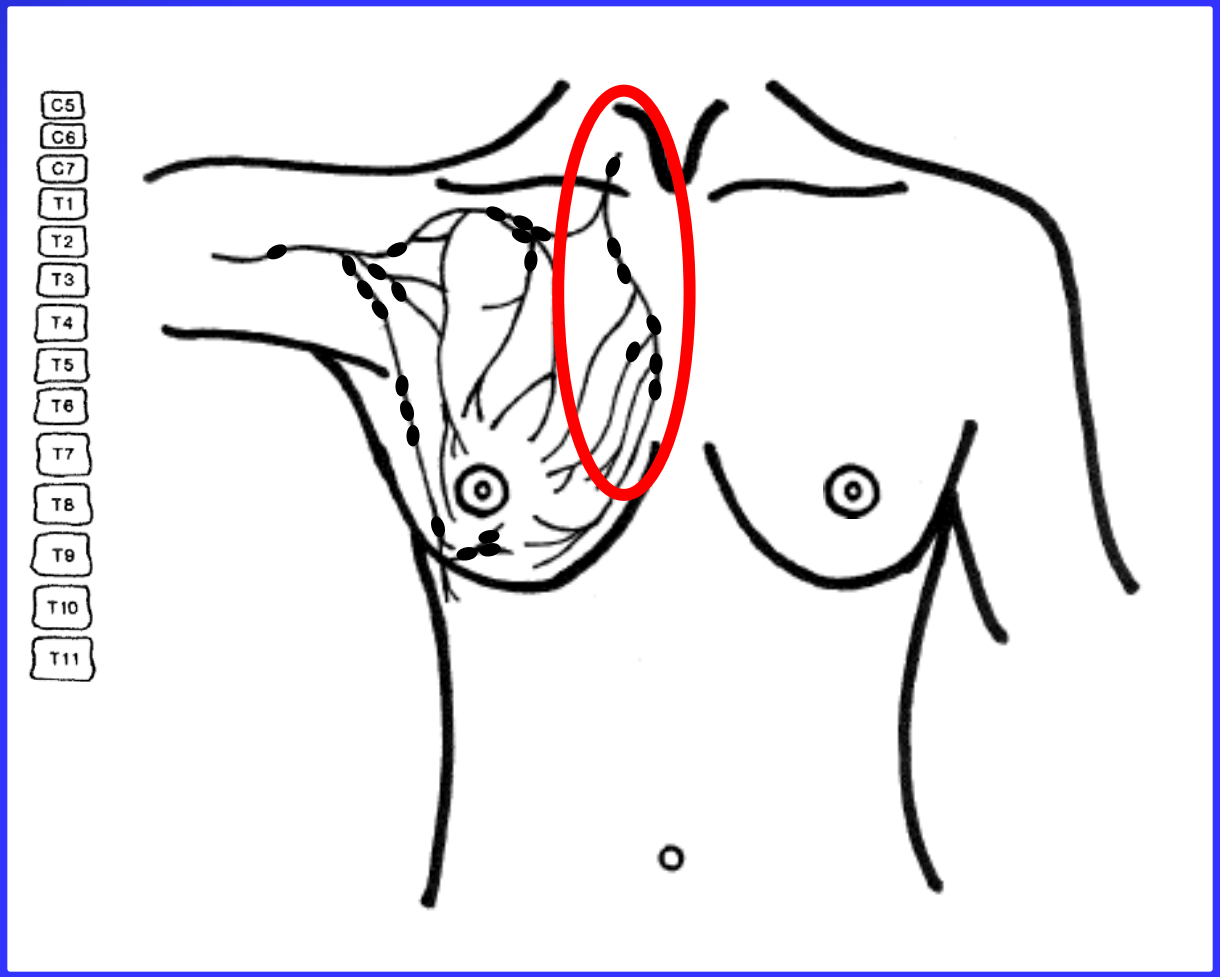
Second GI Cancers Study: Methods

- Medical record abstraction
  - Breast/esophageal cancer diagnoses
  - Breast cancer treatment data
    - Radiotherapy, chemotherapy, hormonal agents
  - Smoking, alcohol, BMI, family history of cancer
- Detailed radiation dosimetry
- Conditional logistic regression analysis

Morton *et al.*, Submitted

Radiation Dosimetry

25 points of dose calculation along the esophagus



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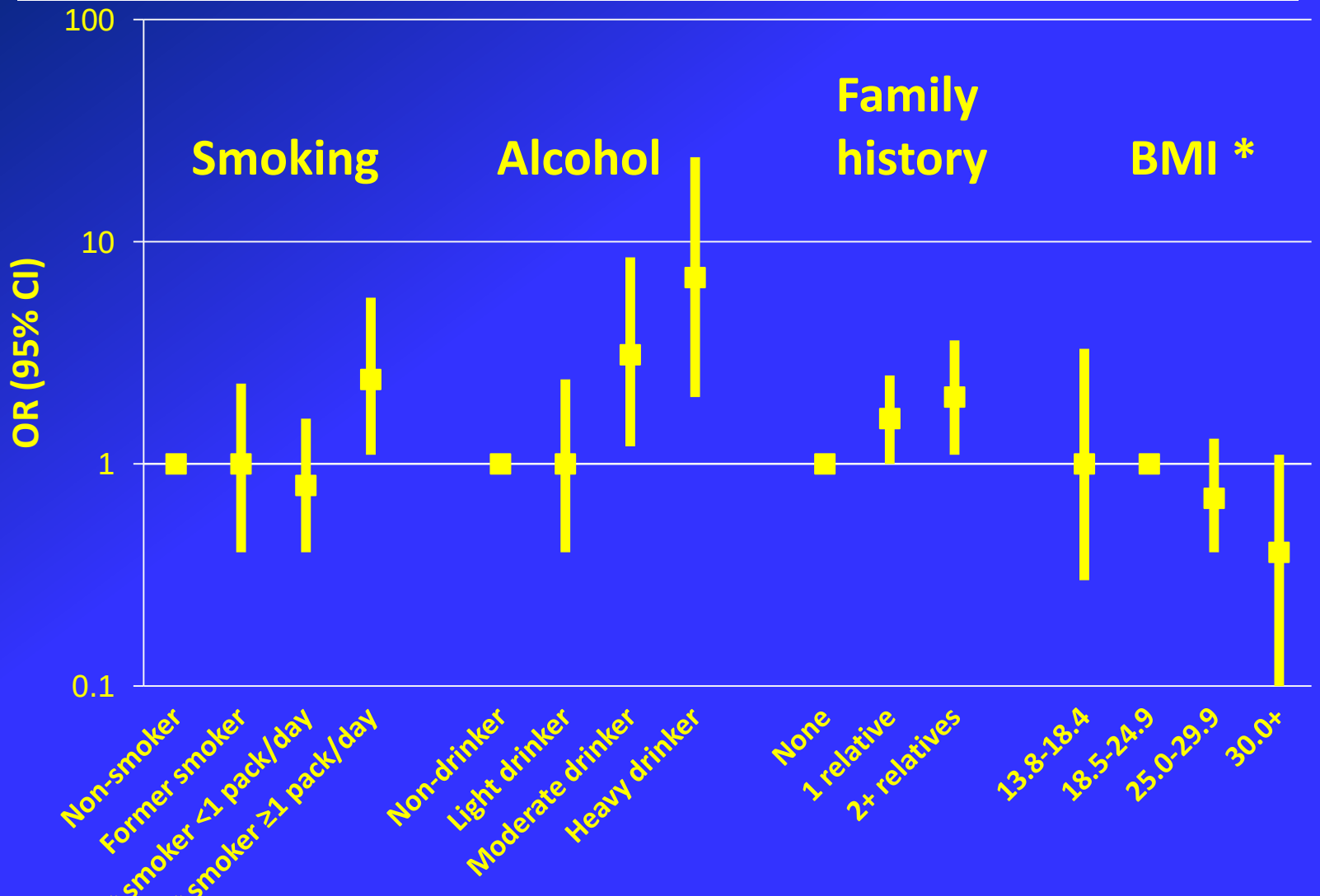
Results: Radiotherapy

	Cases	Controls	
Dose (Gy) *	N	N	OR(95% CI)
0	84	201	1.0 (referent)
0.1-4.9	47	117	0.9 (0.6 to 1.5)
5.0-9.9	22	35	1.6 (0.8 to 3.2)
10.0-19.9	20	31	1.9 (0.9 to 3.9)
20.0-29.9	48	60	2.8 (1.6 to 4.9)
30.0-44.5	19	13	4.9 (2.0 to 12)
P_{trend}			<0.001
EOR/Gy			0.08 (0.04 to 0.16)

* Dose to the midpoint of the tumor.

Morton *et al.*, Submitted

Results: Non-Treatment Risk Factors



Morton *et al.*, Submitted

* Risks presented for esophageal squamous cell carcinoma only.

Comment

- First study to provide quantitative radiation dose estimates to the esophagus after radiotherapy for breast cancer
- Dose-response compatible with linearity
  - EOR/Gy = 0.08, lower than patients treated for ankylosing spondylitis or in the LSS
- Data consistent with multiplicative effect of radiation and other esophageal cancer risk factors

Morton *et al.*, Submitted

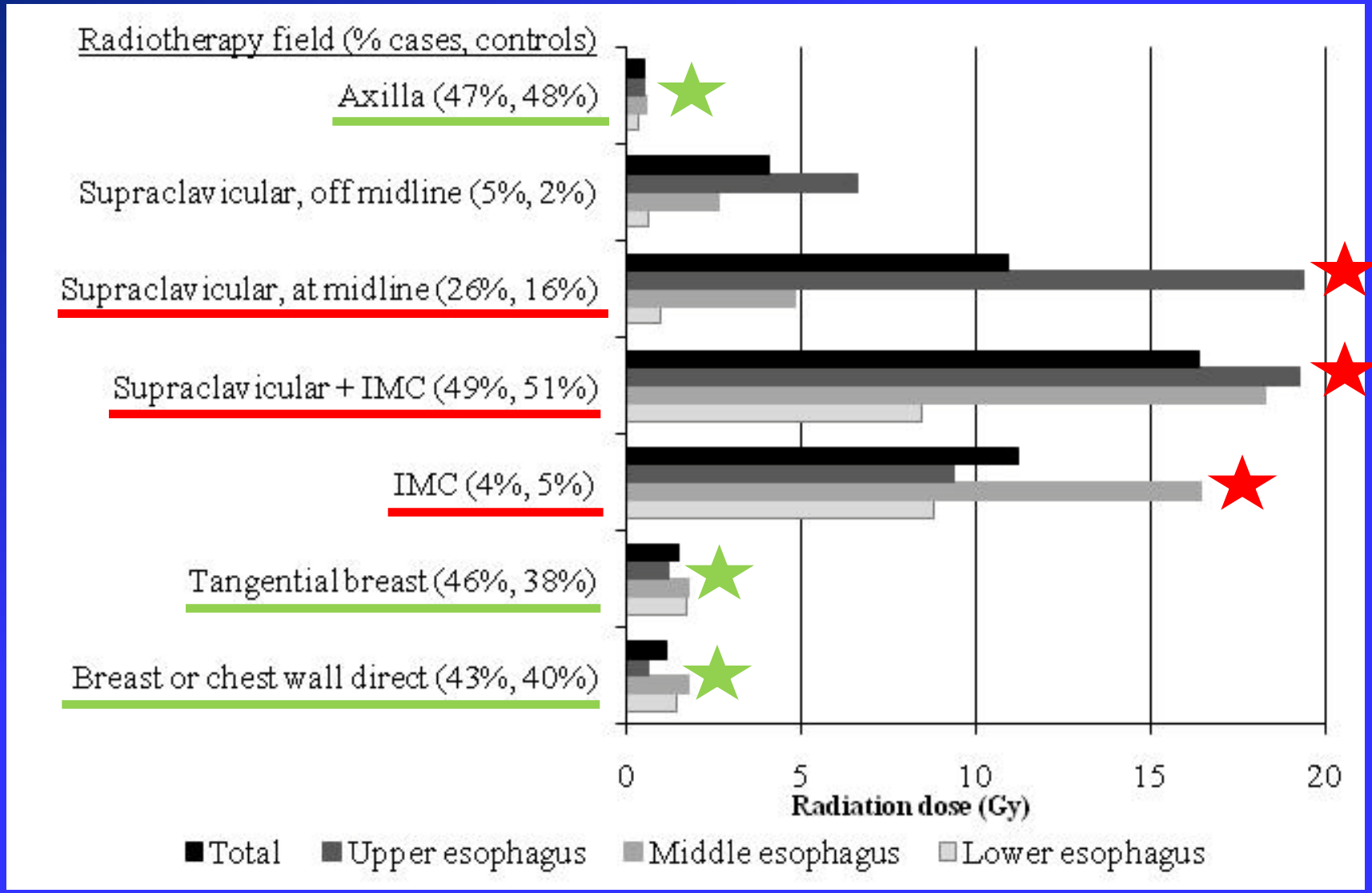
Comment

- Low absolute risk: 5 excess cases/1000 women due to radiation over 25 years
  - aged 60, receiving 30 Gy to the esophagus

- Consider dose to the esophagus in radiation treatment planning
- Provides quantitative information for risk/benefit calculation for radiotherapy
- Certain treatment practices have changed

Morton *et al.*, Submitted

Radiotherapy Fields



Morton *et al.*, Submitted

Comment

- Increased patient and clinician education regarding risks and symptoms of esophageal disease
- Lower threshold for endoscopy
  - Particularly for women with supraclavicular and IMC irradiation and other esophageal cancer risk factors

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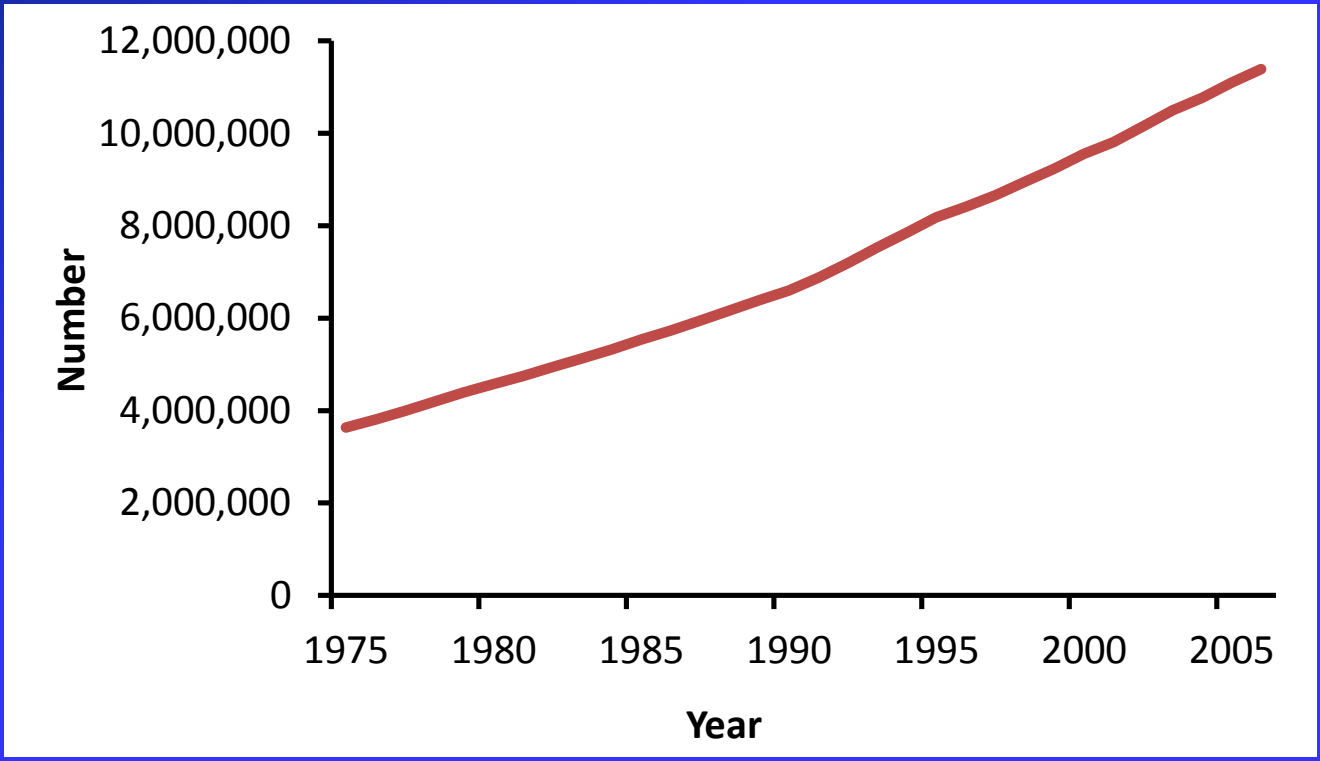
Second Cancers

- >11 million cancer survivors in the US



- 1 in 6 cancers diagnosed today in a cancer survivor

Second Cancer Risk Factors

- Radiotherapy accounts for ~8% of second cancers (Berrington de Gonzalez et al. Lancet Oncol 2011)
- >90% second cancers related to:
  - other treatments
  - lifestyle factors
  - medical history
  - genetic susceptibility

Future Directions

- Understand effect modifiers to identify patients at highest risk of radiotherapy-related second cancer
  - New study designs to capture other risk factor data and biospecimens
- Other cancer sites requiring additional study (e.g., colon)
- Mechanisms of carcinogenesis following high-dose radiation exposures

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